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PROCAINAMIDE, OXPRENOLOL AND AMIODARONE AS ANTIDYSRHYTHMIC DRUGS IN MYOCARDIAL INFARCTION

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SUMMARY

Using Holter recordings and based on the principle that most of the survivors of acute myocardial infarction who are going to die suddenly after hospital discharge are those who present ventricular premature beats (VPB), the authors have studied the effect of three different antidysrhythmic drugs — procainamide (PA), oxprenolol (OX) and amiodarones. (AMIOD) — in late phase of acute myocardial infarction. All the trials have been controlled Procainamide (47 patients studied), in comparison with placebo (PL), revealed to be effective (a) in supressing and diminishing VPB/hour (p=0.0425), and (b) in maintaining patients with no VPB (PA 89.6% — PL 64.7%). Oxprenolol (27 patients studied), in comparison with placebo, revealed to be effective (a) in maintaining patients with no VPB (p=0.0525), and (b) in avoiding the increase of VPB/hour (p=0.0576). Finally amiodarone (37 patients studied), in comparison with placebo, was effective (a) in maintaining patients with no VPB (AMIOD 50% — PL 39%), (b) in diminishing VPB/hour (AMIOD 29% — PL 9%), and (c) in avoiding the increase of VPB/hour (AMIOD 79% — PL 48%). The authors finish their paper emphasizing that no antidysrhythmic drug should be introduced in clinical practice before being submitted to controlled studies with Holter electrocardiography.

Several studies have shown that frequent ventricular premature beats (VPB) are the cause of severe ventricular arrhythmias — Ventricular Tachycardia and Ventricular Fibrillation — and can therefore be accounted responsible for sudden death (1, 2, 3, 5, 6). On the other hand there are some studies with Holter electrocardiography from which we conclude that most of the survivors of acute myocardial infarction who are going to die suddenly after hospital discharge are those who present ventricular extra-systoles (5, 6, 7, 9, 10).

Holter recordings may be important in the follow-up of post-myocardial infarction patients in two particular fields:

1. identification of patients prone to sudden death (presence of ventricular premature beats during 2nd and 3rd weeks after acute myocardial infarction); and
2. evaluation of the effectiveness of antidysrhythmic drugs.

Based on these principles we have used the continuous ambulatory recording of the electrocardiogram to study the effectiveness of oxprenolol, procainamide and amiodarone in subacute phase of myocardial infarction. It is important to emphasize that drugs which are effective during the acute phase of myocardial infarction — lignocaine, for example — are of no effectiveness during the 2nd and 3rd weeks of the evolution of infarction, and this is the reason why we have studied the above mentioned drugs.

All the patients to whom the drugs have been given were in subacute phase of myocardial infarction, as previously said, and they weren't submitted to therapy neither with digitalis nor with other antidysrhythmic drugs.

All the trials have been controlled ones (8). After the randomization we have proceded to double-blind studies with a comparison group of patients on placebo (with or without crossing-over depending on the study), and finally we have submitted our results to statistical analysis requiring a significance of $p \leq 0{,}05$.

I. *Procainamide Trial*

The material consisted of substance of subacute myocardial patients, and the trial started between the 5th and 8th day of the evolution of the disease. We have selected patients in the groups I, II and III of the classification of Killip and Kimball (1967), with no contraindication for procainamide treatment.

The study protocol was as it follows:

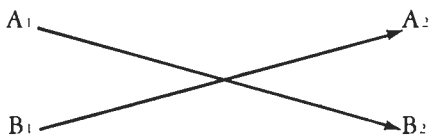
1st day — 1st Holter recording;
2nd day — procainamide or placebo was started;
5th day — 2nd Holter recording;
6th day — change of drug (crossing-over);
9th day — 3rd Holter recording.

The oral route was used, and procainamide dosage has been the following, according to the patient's weight:

1st dose (loading dose) — 1000 mg
Following doses:

<60 Kg — 375 mg every four hours (2250 mg by day);
60-80 Kg — 500 mg every four hours (3000 mg by day);
>80 Kg — 625 mg every four hours (3750 mg by day).

Randomization and crossing-over provided two groups of patients: $A_1 - B_2$, and $B_1 - A_2$.

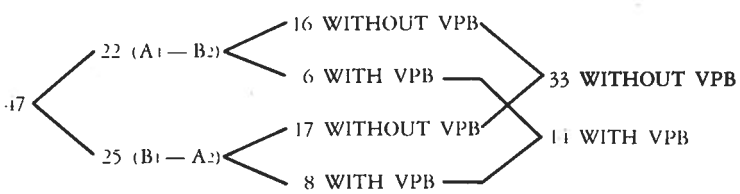


The meaning of the used code was as follows: A_1 was procainamide when it was the first drug to be given, and B_1 was placebo when it was the first drug to be given; A_2 was procainamide when it was the second drug to be administered and B_2 was placebo when it was given as a second medicine.

From the initial 68 patients we have only submitted 47 to statistical analysis: 21 patients were excluded because of some problems with Holter recordings (recordings which were not performed, and tapes which were impossible to scan on account of artefacts).

The following paragraphs summarize the course of events of the trial and its results:

(a) *Distribution of patients according to the existence or non-existence of VPB at the time of 1st Holter recording.*



(b) *Statistical data on patients without VPB all the time.*

A_1=15/16=0.93750	A_1+A_2=24/27=0.8889
B_1=11/17=0.6470	B_1+B_2=20/32=0.6250
A_2= 9/11=0.8182	$A_1+A_2+A'_2$=26/29=0.8966
B_2= 9/15=0.6000	$B_1+B_2+B'_2$=22/34=0.6471

The symbols A'_2 and B'_2 appear for the first time in this paragraph.
The first one refers to the treatment A_2 when performed in patients initially with VPB but with no VPB after B_1: in the same way B'_2 refers to patients on B_2 treatment when it was performed in cases initially with VPB, but with no VPB after A_1.

(c) *Disappearance of VPB*

A_1=3/6 =0.500	A_1+A_2=8/18=0.444
B_1=2/8 =0.250	B_1+B_2=4/12=0.333
A_2=5/12=0.417	
B_2=2/4 =0.500	

(d) *Reduction of frequency of VPB*

A_1=3/6 =0.500	A_1+A_2=8/18=0.444
B_1=1/8 =0.125	B_1+B_2=4/12=0.333
A_2=5/12=0.417	
B_2=0/4 =0.000	

(e) *Associating the disappearance and the reduction of frequency of ventricular premature beats we may now speak about the beneficial effect of the drug:*

«*Possible beneficial effect of procainamide*»

A_1= 6/6 =1.000	A_2=10/12=0.833	A_1+A_2=16/18=0.889*
B_1= 3/8 =0.375	B_2= 2/4 =0.500	B_1+B_2= 5/12=0.417

* p=0.0125 possible beneficial effects of procainamide

From these data we may conclude that there is a significative difference between the effectiveness of procainamide and placebo.

(f) *Conclusions of procainamide trial*

1st — PROCAINAMIDE, in comparison with PLACEBO, revealed to be effective
(a) in suppressing and diminishing VPB/H (P+0.0425), and
(b) in maintaining patients with no VPB (89.6% PA — 64.7% P)
2nd — No side effect was detected with used dosage during the period of trial.

II. *Oxprenolol Trial*

We are going to present now, in an abridged form, the results of our study with the beta-blocker oxprenolol administered by oral route.

It was a controlled study as well. The main differences in relation to the procainamide trial were that patients were of the classes I and II of Killip and Kimball, with no contraindication to beta-blockers, and there was no crossing-over: we only had a comparison group of patients under the action of placebo.

From the 40 initial patients we've only submitted 27 to statistical analysis for reasons that were similar to those invoked to put out of study some cases in the procainamide trial (patients who did not perform all the Holter recordings, and patients whose tapes were in a condition not good enough to be scanned).

In the two following paragraphs we mention the statistical data and the conclusions of the oxprenolol trial.

1. *Statistical data*

	NO VPB ALL THE TIME*	↓ VPB	↑ VPB**	TOTAL OF PATIENTS
OXPRENOLOL	10	3	3	16
PLACEBO	5	—	6	11
TOTAL OF PATIENTS	15	3	9	27

* p=0.0525 (5.25%)

** p=0.0576 (5.76%)

These are small numbers but we emphasize that they were considered suitable for statistical analysis. Although the significance we have obtained is not within the required limits it is only very slightly under those limits.

2. *Conclusions of oxprenolol trial*

1st — OXPRENOLOL, in comparison with PLACEBO, revealed to be effective
(a) in maintaining patients with no VPB (p=0.0525); and
(b) in avoiding the increase of VPB/H (p=0.0576)
2nd — No significant side effect was noticed with used dosage (2 mg/Kg/day) during the period of trial (7th — 10th day of myocardial infarction, plus 6 days).

III. *Amiodarone Trial*

Amiodarone trial, which is not yet completely finished, will be our last controlled study to be presented. Patients were of the classes I and II of Killip and Kimball and the drug was compared with placebo: there was no crossing-over which would be tremendously difficult, or even impossible, in the particular case of this drug on account of its carry-over effect.

Amiodarone was administered «per os»in the following dosage:

— first 2 days — 5×200 mg by day;
— next 4 days — 3×200 mg by day;
— following days until 30th day — 2×200 mg by day.

Up to now we have concluded the findings on the antidysrhythmic aspects of the drug. Our studies on side effects and other pharmacological characteristics of amiodarone are now being subjected to analysis for publication.

From 37 studied patients we may extract the following conclusions.

AMIODARONE, in comparison with PLACEBO, revealed to be effective:

(a) in maintaining patients with no VPB (amiodarone 50% — placebo 39%);
(b) in diminishing VPB/hour (amiodarone 29% — placebo 9%);
and
(c) in avoiding the increase of VPB/hour (amiodarone 79% — placebo 48%).

Although the relatively low incidence of ventricular arrhythmias in the population we have studied, our three trials on the antidysrhythmic effect of procainamide, oxprenolol and amiodarone, authorize us to conclude that those three drugs are potentially useful in subacute phase of myocardial infarction.

To put an end to this publication we would like to emphasize that in our opinion no antidysrhythmic drug should be introduced in clinical practice before being submitted to controlled studies with Holter electrocardiography.

RESUMO

PROCAINAMIDA, OXPRENOLOL E AMIODARONA COMO DROGAS ANTIDISRÍTMICAS NO ENFARTE DE MIOCÁRDIO

Baseando-se no princípio de que a maior parte dos sobreviventes de enfarte agudo do miocárdio que vão morrer subitamente após a alta hospitalar são os doentes que apresentam extra-sístoles ventriculares (EV), os autores estudaram o efeito de três fármacos antidisrítmicos diferentes — PROCAINAMIDA (PA), OXPRENALOL (OX), e AMIODARONA (AMIOD) — na fase tardia do enfarte agudo do miocárdio, recorrendo às gravações de Holter. Todos os estudos foram controlados. A PROCAINAMIDA (47 doentes estudados), em comparação com o Placebo (PL), revelou-se um fármaco efectivo (a) na supressão e na diminuição do número de EV/hora (P=0,0425), e (b) e na manutenção de doentes sem EV (PA — 89,6% vs PL 64,,7%). O OXPRENOLOL (27 doentes estudados), em comparação com o Placebo, revelou-se ser eficaz (a) na manutenção de doentes sem EV (p=0,0525), e (b) em evitar o aumento do número de EV/hora (p=0,0576). Finalmente a AMIODARONA (37 doentes estudados), comparada com o Placebo, foi eficaz, (a) na manutenção de doentes sem EV (AMIOD 50% vs

PL 39%), (b) na diminuição do número de EV/hora (AMIOD 29%, vs PL 9%), e (c) em evitar o aumento do número de EV/hora (AMIOD 79% vs PL 48%). Os autores terminam a sua publicação realçando que qualquer droga antidisrítmica só deverá ser introduzida na prática clínica depois de submetida a estudos controlados com recurso à Electrocardiografia de Holter.

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